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### Permalink

<https://escholarship.org/uc/item/9r1859bf>

### Journal

Pediatric neuroscience, 13(1)

### ISSN

0255-7975

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### Publication Date

1987

### DOI

10.1159/000120301

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## Encephalopathy in a 14-Year-Old Boy with Leukemia in Remission

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### Clinical History

This boy was well until the age of 12 years when he developed a cough. A month later he was treated with antibiotics for fever, anorexia and vomiting without improvement. A film of peripheral blood showed blast cells. Examination on admission showed him to be tired and unwell. Hemoglobin was 10.9 g/%, white blood cell count (WBC) 10,800/ $\mu$ l with 7% polymorphs, 7% stab cells, 80% lymphocytes and 6% blasts, and platelet count was 154,000/ $\mu$ l. Examination of the bone marrow showed a marked infiltrate of blast cells. Of the blast cells 95% were positive for common acute lymphoblastic leukemia (ALL) antigen. His cerebrospinal fluid (CSF) contained 20 erythrocytes (RBC)/ $\mu$ l and 6 WBC/ $\mu$ l, but no blast cells. He received the following induction chemotherapy: vincristine, 2 mg i.v. 4 times weekly; daunomycin, 35 mg i.v. 4 times weekly; L-asparaginase, 8,400 U i.m. for 9 doses; prednisone, 30 mg 3 times daily for 28 days, and intrathecal methotrexate 12 mg twice. He did not receive cranial irradiation. He tolerated the chemotherapy well; by day 14 his bone marrow was in remission, and by 28 days, hypocellular. He was treated with intravenous cloxacillin and gentamicin for fever. When various cultures were negative antibiotics were stopped.

He had low back pain due to osteoporosis and slight collapse of the end plates of L<sub>1</sub> and L<sub>2</sub> vertebrae. He passed a renal calculus attributed to bone demineralization secondary to prednisone. Consolidation therapy consisted of cyclophosphamide, 1,350 mg for 2 doses, 6-mercaptopurine (6-MP), 80 mg daily for 27 days, Ara-C, 100 mg s.c. 4 times a week for 4 weeks, and intrathecal methotrexate weekly.

Over the next 2 years he was maintained on 6-MP, vincristine, prednisone and intrathecal methotrexate every 3 months. Several episodes of neutropenia and thrombocytopenia resulted in his chemotherapy being withheld for short periods of time. His bone marrow remained in remission. His CSF was normal. Several episodes of infection required treatment with antibiotics.

Thirty months after the diagnosis of leukemia was made, and 3 months before his last admission, he was admitted with cough productive of yellow sputum, fever and vomiting. He had been continued on 6-MP and intrathecal methotrexate. His temperature was 39.8 °C, and he looked unwell. Chest X-ray showed a widespread interstitial pneumonia. WBC was 1,800/ $\mu$ l with neutrophils 1,296/ $\mu$ l, band cells 198/ $\mu$ l, lymphocytes 99/ $\mu$ l, monocytes 72/ $\mu$ l, eosinophils 99/ $\mu$ l, metamyelocytes 18/ $\mu$ l, and atypical lymphs 18/ $\mu$ l.

Hemoglobin was 13.5 g/%, and platelet count 79,000/ $\mu$ l. His serum was tested for antibodies to various viruses, including measles, and all were negative. A lung biopsy showed *Pneumocystis carinii*. Septa was increased, and he was continued on ampicillin and gentamicin. He was discharged home, but readmitted a few days later.

He was then hospitalized for 2 weeks because of fever, neutropenia and an intermittent scaly skin rash, which did not look like measles. Measles were present in the community. Chemotherapy had been withheld for 10 days prior to this admission because of neutropenia. Physical examination showed a red pharynx and a few petechiae on the soft palate. Chest X-ray showed increased interstitial markings. Treatment with gentamycin, cloxacillin and Bactrim did not improve his state, so he was treated with cefuroxime, amantadine and amphotericin. He became afebrile and was discharged.

Several days later he was readmitted with a high, spiking fever and dry cough. Investigations showed only a mild persisting interstitial pneumonitis. A bone marrow aspiration showed 1% blast cells. He was pancytopenic. A second lung biopsy was performed. The lung biopsy showed a nodular interstitial pneumonitis, with scarring, obliteration of the air spaces, nodules of proliferating bronchiolar lining cells, macrophages and a few polymorphonuclear leukocytes. Multinucleate giant cells were present. Stains for organisms and electron microscopy failed to show any microorganisms or viral inclusions. Cultures for virus were negative. He was discharged after a few days.

His last admission was for persistent respiratory problems. The patient had been cooperative previously; several days after his admission he was rude and uncooperative. Three days later he became confused and reported 'a girl stealing Fruit Loops' and could subtract serial 7s only to 86. He had oral candidiasis. His WBC was 3,200/ $\mu$ l and hemoglobin 10.1 g/%. A spinal tap 2 days after the onset of his confusion showed that the CSF was under normal pressure, clear and colorless. Measles antibody titers for IgG and IgM in the CSF were negative. The protein was 36 mg/dl, glucose 26 mg/dl, RBC 1/ $\mu$ l, and nucleated cells 0. He was treated with an intravenous infusion of gamma globulin. Over the next few days he made inappropriate comments, was confused, slow and anorexic. Then one leg twitched repeatedly through the morning. He became disoriented and had little memory of the events of the previous few days. These were considered as possible episodes of myoclonus. The patient reported twitchings of the right lower leg, which he could suppress only with great difficulty.

He had a fever of 38.5 °C. EEG showed a disorganized background, occasional multifocal sharp waves, including polyspike discharges and epileptiform discharges. Focal lesions were not evident on computed tomography (CT) scan, although global tissue loss was noted. There was no improvement despite therapeutic doses of diphenylhydantoin. Six days after he was first confused he became drowsy.

Ten days after the onset of confusion he complained of a burning sensation in the right eye and vomited several times. The next day he developed generalized, multifocal, myoclonic jerking of the legs, right arm and head. He complained of pain in the right ear. He was drowsy but coherent. The next day, all four limbs twitched uncontrollably. He was conscious and oriented, but not appropriately upset about the twitching. He tried to hold a cup of tea although his twitching was too great to do so. He was treated with interferon, 20 MU daily for 4 weeks. Two weeks after he first became confused he was drowsier, his speech was slurred but coherent. He was oriented to place but not to date, and was so drowsy that his memory could not be tested. Myoclonic jerking was improved, but both feet twitched. He was on diphenylhydantoin, 150 mg twice daily, and Ativan as required. He was drowsier. He had *epilepsia partialis continua*.

Three weeks later he developed a morbilliform, maculopapular, erythematous rash over the legs, feet and back; it was scant over the arms. The differential diagnosis was drug rash or measles-like rash. It was not a classical rubella rash. A month after onset of neurological symptoms he had his first generalized tonic-clonic seizure. He cried out for help, and started twitching. A patchy, acute, superficial retinitis was resolving. The retina showed only minor pigmentary abnormalities.

Five weeks after the onset of neurological symptoms he became unresponsive. The only response to painful stimuli was vague opening of the eyes and increase in respiratory rate. Pupils were round, equal and symmetrical, eyes conjugate, and eye movements roving and full, with no nystagmus. He was hypotonic with decreased deep tendon reflexes and upgoing plantar responses. He developed congestive heart failure and was treated with digoxin. He was febrile and dusky, with increasing densities in the right lower and right middle lobes, and had air hunger. *Septera* was increased.

He was transferred to the intensive care unit. He was treated with erythromycin and placed on a respirator. He was given dopamine, saline and plasma intravenously, to support his blood pressure.

The retinitis showed healing areas, but also new acute lesions. Hemoglobin was 9.9 g/% (after transfusion), platelets 57,000/ $\mu$ l, WBC 10,400/ $\mu$ l with lymphocytes 600/ $\mu$ l. He was maintained with continuous positive airway pressure.

Seven weeks after the onset of neurological symptoms he was comatose. Both arms twitched independently. This was described as multifocal seizures, *epilepsia partialis continua* and myoclonic jerks. He was unresponsive to deep pain. Pupils were 2–3 mm and reacted sluggishly. Eye movements were full, and corneal reflexes were present. There was no response to suctioning, all limbs were flaccid, tendon reflexes were depressed and plantars showed no response. He was on a respirator, but breathing spontaneously, with improved cardiorespiratory function.

He was extubated and transferred back to the ward, where he was maintained on anticonvulsants, antibiotics, oxygen and total parenteral nutrition. He had occasional right-sided seizures. He developed various complications, including a decubitus ulcer, hypernatremia attributed to hyperaldosteronism, congestive heart failure and

hypocalcemia. About 2 months after the onset of neurological symptoms he developed further deterioration in his lung function, with development of rales, rhonchi and decreased air entry in the right side. It was decided that no further therapy was warranted except palliative care. Death occurred almost 3 months after onset of neurological symptoms.

Investigations: IgG 290 mg/dl (normal 750–2,000), IgA 32 mg/dl (normal 84–483), IgM 19 mg/dl (normal 63–250). IgG in the CSF was 1.7 ng/dl. Viral serology 4 days and 2 weeks after the administration of gamma globulin showed the IgG to be measles-positive, the IgM negative; this was considered to be passively acquired antibody due to the administration of gamma globulin.

The mother did not know whether the boy had had measles immunization, and could not find this out despite persistent questioning.

### Discussion: Dr. T.Z. Baram

This case presentation deals with a subacute neurological deterioration in a 14-year-old boy 2 years after the diagnosis of ALL. In summary, having been found to have ALL, this young gentleman received the accepted treatment for leukemia: induction (with vincristine, daunomycin, *L*-asparaginase, prednisone and intrathecal methotrexate); consolidation (with Cytosan, 6-MP, Ara-C); intrathecal methotrexate for central nervous system (CNS) prophylaxis and maintenance (6-MP, vincristine and prednisone).

We are told of several of the not uncommon complications of leukemia and its treatment, such as osteoporosis with a mild compression of L<sub>1</sub> and L<sub>2</sub> vertebrae, as well as neutropenia, thrombocytopenia and infections. Specifically absent from the case presentation is information about the administration of blood transfusions.

The case presentation becomes more detailed 3 months prior to the youngster's last admission, when he presented with yellow sputum, fever and vomiting, had an interstitial pneumonitis diagnosed as *P. carinii*, for which he was treated. Subsequent episodes of fever and neutropenia with an unusual scaly skin rash and soft palate petechiae followed, with a questionable responsiveness to the combination of cefuroxime, amphotericin B and amantadine. During the subsequent admission for interstitial pneumonitis, open-lung biopsy was performed.

His neurological deterioration is detailed in the description of his last admission. That consisted of a personality change, specifically rudeness, confusion and hallucinations, followed by a movement disorder, probably myoclonus, with an abnormal EEG and atrophy on CT scan. Over 2 months his neurological

status declined with drowsiness, dementia and worsening of the myoclonus. Terminally, he was unresponsive with normal pupils, full eye movements, hypotonia and extensor plantar responses; diffuse multifocal myoclonus is described. Throughout the last month of his illness he had a retinitis. Decompensation of cardiac and pulmonary functions with a probable superimposed infection occurred, to which the youngster succumbed.

In short, a youngster with leukemia, suffering the effects of the disease and its treatment, undergoes progressive neurological deterioration over a 3-month course, resulting in death.

In discussing possible causes for our patient's neurological deterioration, several issues need to be considered: the effects of ALL per se on the CNS; the direct effects of drugs used for its treatment, and the indirect effects of therapy, i.e. the presence of an immunocompromised state.

The patient was in remission, with no malignant cells in his CSF, and had received CNS prophylaxis. It is thus unlikely that he had CNS leukemia. Moreover, CNS leukemia usually manifests the effects of meningeal involvement, and increased intracranial pressure was not seen in our patient [1].

It is unlikely also that the subacute neurological decline of the patient was due to chemotherapy. Vincristine usually causes peripheral neuropathy, but has well-documented CNS effects on humans, in animal studies and on neurons in vitro [2-4]. *L*-Asparaginase has been associated with stroke-like episodes [5]. High doses of Ara-C result in cerebellar ataxia as well as diffuse, global neurological dysfunction [6,7]. Methotrexate, used either in high doses systemically, or intrathecally, has been shown to result in acute stroke-like episodes with hemiplegia, seizures and aphasia [8, 9]. Methotrexate has also been associated with subacute deterioration in mental status and diffuse global dysfunction [8, 10].

These toxic effects are acute and immediate and unlikely to occur as late in the course as our patient was; however, long-term effects of chemoprophylaxis for CNS leukemia merit consideration [11, 12]. These, more common with radiation therapy but seen with intrathecal methotrexate alone, present as a subacute leukoencephalopathy (e.g. confusion, lethargy, ataxia, spasticity) [12, 13]. Unlike the findings with subacute leukoencephalopathy [14], our patient's CT revealed only cerebral atrophy, found in 16% of children given intrathecal methotrexate [15].

Throughout his illness, our patient had fever, with clinical and pathological evidence for several infections. ALL and its treatment cause an immunocompromised state. Thus, youngsters on therapy for ALL have a susceptibility to a host of opportunistic organisms. Bacterial infections, notoriously *Pseudomonas*, *Klebsiella* and *Escherichia coli*, usually run an acute fulminant course [16]. The CNS is involved directly or indirectly (as a result of anemia, hypoxia or sepsis) [16, 17]. This patient's prolonged, gradual deterioration does not suggest an acute bacterial infection. Rarely, a subacute or chronic course is seen with unusual bacterial disease, such as CNS Whipple, described in immunocompromised patients with AIDS [18]. Its manifestations include movement disorders, such as the myoclonus seen in our patient [18]; however, prominent dysfunction of ocular motility, absent in this case, has been a persistent finding in CNS Whipple [18, 19].

This patient's immunodeficiency, antibiotic treatment and chronic course of fever and CNS decline are compatible with a fungal infection. Oral candidiasis was present during his last admission. *Candida* has recently emerged as the most common fungal CNS infection in the immunocompromised host [16, 20]. A recent review [20] suggests that the CNS is involved in 50% of systemic *Candida* infections, yet this CNS involvement is rarely suspected or proved antemortem. The neurological involvement and manifestation of *Candida* can be protean and can fit with this patient's course. Still, CNS candidiasis is usually associated with fulminant systemic disease [20], and the absence of *Candida* on lung biopsy would be unusual. Other neurotropic fungal infections such as cryptococcosis and actinomycosis would have been detected on CSF studies and/or lung biopsy [21].

Protozoal parasites infect immunocompromised hosts, specifically, *P. carinii* and *Toxoplasma gondii* [22]. The former, isolated from the patient's lungs, only rarely invades the CNS [16]; toxoplasmosis results in a necrotizing encephalitis and, commonly, typical ocular involvement, not present in this case [16].

We are left with a viral infection, which I consider as the most likely etiology for this patient's course.

Prior to discussing the host of viruses which may involve the CNS in the immunocompromised host, a review of some of the clues provided by the case presentation may be indicated. Fever, a morbilliform rash and palatal petechiae are nonspecific; the lung biopsy findings and the retinitis are more helpful. The lung biopsy revealed airway obliteration, interstitial pneumonitis

and multinucleated giant cells. The latter had been described as typical for measles infection by Hecht in 1910 [23]. Very few other organisms, notably respiratory syncytial virus, can create this pathological appearance [J.M. Bruner, pers. commun.]. The absence of viral inclusions does not rule out a measles pneumonia.

Superficial patchy retinitis has been described with numerous viruses [26]. The large herpesviruses, namely cytomegalovirus (CMV), herpes simplex and varicella-zoster, as well as the measles virus may cause lesions with identical funduscopy and histologic appearance [26]. Retinitis is commonly the presenting feature of subacute sclerosing panencephalitis (SSPE) and occurs at some point in 50% of patients [25, 26]. The presence of both healing and new lesions is very typical of SSPE [R. Lewis, pers. commun.]. The retinopathies of congenital measles virus, progressive measles infection and SSPE may be indistinguishable [24]. Thus, the lung findings and, to some degree the funduscopy examination, as well as the rash, may suggest infection with measles virus.

Measles virus infection in the human can result in three types of infections. The most common, in an immunocompetent host, is the familiar acute disease, with Koplik's spots, fever, coryza and rash. Rarely, this may be followed by a measles encephalitis. In the immunocompromised host, an 'atypical' infection has been reported, with an acute or a subacute course associated with progressive involvement of lung and CNS [23, 27, 28]. Atypical measles with encephalitis is seen in children with leukemia [27–29] and lymphoma, commonly in remission [27, 28], or other chronic illnesses [28]. Measles infection precedes the neurological deterioration by weeks to 6 months; the latter is characterized by personality changes [27, 29], seizures [27, 28], commonly myoclonic seizures [30, 31] or epilepsy partialis continua [29], declining mental status and death [27–31]. The course simulates an accelerated version of that of SSPE [28]. Neurologic dysfunction can be acute, with death occurring within a week of presentation [28], but more commonly is subacute, with death 4–10 weeks after onset [29–31]. CSF and serum IgG and measles titers in these immunodeficient patients are unpredictable: of 11 patients mentioned in these series [23, 27–31] in whom CSF and/or serum measles titers were obtained, only 5 were positive. The criteria for the diagnosis of progressive measles encephalitis are: measles infection in an immunocompromised host, followed by progressive encephalopathy, in conjunction with demonstration of measles virus (by immunofluores-

cence, electron microscopy or culture) on biopsy or autopsy.

The third type of human involvement with measles virus is associated with a remote infection, usually in infancy, followed years later by neurological deterioration with personality change, dementia, myoclonic seizures, coma and death. This SSPE is caused by a 'defective' measles virus demonstrable on brain biopsy or autopsy [32]. The clinical course of SSPE has been exhaustively reviewed [20, 33]. The initial presentation is that of mild intellectual deterioration and personality changes with progression of myoclonic seizures. Neurological impairment is progressive, resulting in profound dementia, spasticity, bulbar signs, cortical blindness, and, finally, a vegetative state. The EEG is characteristic with synchronous paroxysmal bursts of 2–3/s high-voltage, diphasic spike waves [33, 34]. The background may be normal early, but slowing and suppression bursts are seen at a later stage. Atypical and even normal (early) EEGs are not uncommon [34].

CSF and serum usually reveal high elevated IgG [33] measles titers. SSPE usually results in death years after onset, but marked variation, including an acute, catastrophic course, has been reported [35].

In the immunocompromised host, the two separate entities of SSPE and progressive measles encephalitis (PME) may blend [28]. In fact, several patients, first reported as having SSPE, were reclassified as having PME [28]. Titers are unhelpful in the immunodeficient [27–31]; the classical cellular reaction (perivascular cuffing) typical for the SSPE brain may be missing [23, 28]. The clinical course and EEG findings may be quite similar.

Murphy and Yunis [28] suggest that the two entities be separated on the basis of the remoteness of initial infection (years versus weeks), immunocompetency and rapidity of clinical course.

I think our patient had measles virus involvement of skin, lungs, retinae and CNS. The absence of measles antibodies early in the course suggests his susceptibility to such an infection and the seroconversion after gamma globulin administration is not helpful. Clinically, his course is more compatible with PME than SSPE, and, as mentioned, the pathological findings on brain autopsy may be identical [23, 28]. One may predict the presence of measles antigens on immunofluorescence, inclusion bodies on light microscopy and the typical microtubular nuclear aggregates on electron microscopy [23].

For completeness sake, several acute and subacute



viral infections need to be mentioned. The herpesviruses are common; herpes simplex may cause retinitis, interstitial pneumonitis and an acute encephalitis; varicella-zoster, while responsible for life-threatening pneumonia, does not seem to have a greater predilection for the CNS in the immunocompromised versus a competent host [36]. Meningoencephalitis, absent in this case, is usually seen [37]. CMV, while showing a predilection for immunodeficient patients, causing interstitial pneumonitis, retinitis and encephalitis [36], can usually be easily cultured from lung biopsy, CSF and urine.

Progressive multifocal leukoencephalopathy is usually seen in immunosuppressed adults [38]. The underlying organism is a papovavirus [39]. CT and autopsy reveal patchy white matter destruction [38]; the CT findings and age of our patient make him an unlikely candidate for this entity.

Human immunodeficiency virus (HIV; HTLV-III) has emerged as a major neurotropic virus [40, 41]. Among the groups at risk for the infection are blood transfusion recipients, which may include our patient. Subacute encephalopathy with personality change, dementia and long tract signs has been described in both children [41, 42] and adults [40]. While multinucleated giant cells have been found in brains infected by HIV [43, 44], they have not been described in the lung [45]. Furthermore, the retinal findings of AIDS include cottonwool spots and usually the finding of other opportunistic organisms (e.g. CMV and *Toxoplasma*) [46, 47]. HIV titers are not reported for this patient, but this virus alone would not account for his clinical presentation.

Thus, I would attribute this patient's illness to progressive measles infection.

Finally, the dogma of 'one patient - one diagnosis' may apply to the immunocompetent host. Our patient, like the majority of immunodeficient hosts, may have harbored two or several concurrent opportunistic organisms which contributed to his demise.

Diagnosis: progressive measles infection of immunocompromised host.

### Discussion of Pathological Findings:

Dr. M.G. Norman

At autopsy the brain weighed 1,290 g (normal 1,440 g). The only abnormality on gross examination was slight enlargement of the lateral ventricles with blunting of the corners of the lateral angles. Microscopic examination showed lesions scattered through the

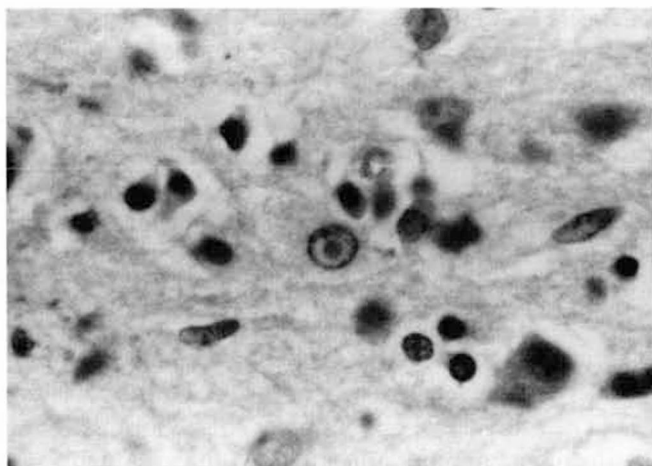
gray matter, mostly in cerebral cortex, with a few in basal ganglia, thalamus, brain stem and cerebellum. These varied from necrosis of individual neurons with a surrounding ring of microglia to somewhat larger areas of neuronal loss, scant microglial reaction and astrocytosis. In some of these foci Cowdry's type A inclusions (fig. 1) were found. In the most severely affected areas there was also some spongy change. In some of these foci, the walls of the vessels were thickened with a few mononuclear inflammatory cells (fig. 2), but infiltrates of plasma cells and lymphocytes in the parenchyma were absent. The curved tubules characteristic of paramyxovirus were found in the brain using electron microscopy. There were no lesions in the white matter, nor was there demyelination. Examination of the eyes showed a mild uveitis, migration of pigment from the retinal pigment epithelium, diminution of peripheral ganglion cells and some foci of loss of the inner nuclear layer as well [J. Rootman, pers. commun.]. Electron microscopy showed the typical curved tubules of paramyxovirus in the retina (fig. 3).

The immediate cause of death was a severe acute bronchopneumonia superimposed on a chronic interstitial pneumonitis with irregular scarring.

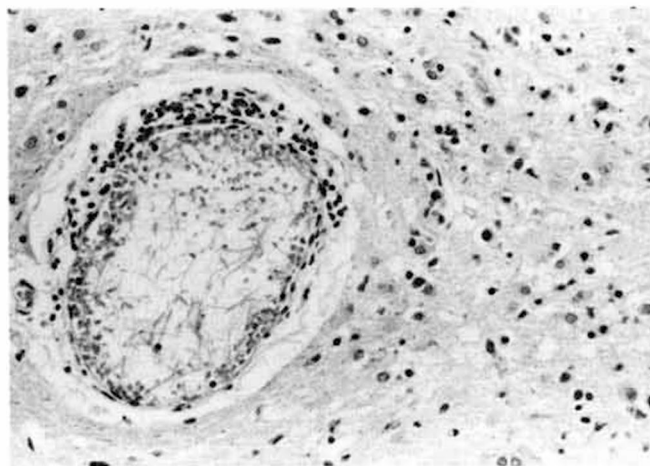
The lymphoid tissue in the lymph nodes, thymus and bowel was depleted with only the reticular framework of the thymus persisting. Germinal centers were absent in the lymph nodes and bowel, and it was difficult to find plasma cells, although a few were present. The marrow was still in remission, but mature polymorphs were depleted, presumably reflecting migration into the acute pneumonia.

About 6 months after this boy died another similar case occurred. A 10-year-old boy with ALL in remission developed an encephalopathy and died. His disease lasted only 1 month. Clinically, it began with difficulty using words; he developed inability to control temperature, hypernatremia and hypertension, as well as dementia, seizures and coma. His serum measles antibody titer was never greater than 1:10. It was known that he had had measles immunization, though not at what age. Although the cerebral cortex was patchily involved, the most damaged part of the brain was the hypothalamus and thalamus, as might have been predicted from his clinical symptoms.

One of the most striking things in these two cases was how little perivascular inflammation was present, in comparison to the usual cases of SSPE. In SSPE there are usually many mononuclear inflammatory cells with abundant plasma cells. It is only in the burned-out cases



**Fig. 1.** Cerebral cortex. Cowdry's type A inclusion in nucleus of astrocytes. Hematoxylin-eosin.  $\times 500$ .

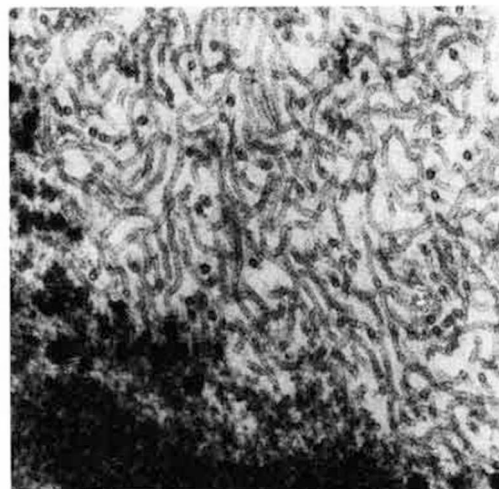


**Fig. 2.** Cerebral cortex. This illustrates maximum degree of mononuclear inflammation. Cells are in vessel wall rather than in surrounding parenchyma. Hematoxylin-eosin.  $\times 100$ .

of SSPE, which have lasted for many years, that inflammatory cells are scant. It is the numerous plasma cells in the cerebral tissue which result in the high CSF measles antibody titers in SSPE.

Gray matter only was affected in our two patients. Cowdry's type A inclusions were present in astrocytes in involved foci, but there was no involvement of white matter, nor any inclusions in oligodendrocytes, as can be seen in SSPE. Whether this indicates any difference in etiopathogenesis between measles in immunosuppressed individuals [sometimes called 'measles inclusion body encephalitis' (MIBE) or 'subacute inclusion body encephalitis' in the immunodeficient individual], or merely reflects the more acute course of MIBE is not known.

The lack of measles antibodies reflects the immune suppression. In both our cases the lymphoid tissue was scant, and only after careful search could any plasma cells be found in lymph nodes, gut and spleen. Since 1959, the failure of children with leukemia in remission with measles giant cell pneumonia to mount an antibody response has been known [48]. The first cases of MIBE were reported in 1973 by Breitfeld et al. [23]. Kipps et al. [49] tabulated the 22 cases of MIBE reported by 1983. Of 15 patients in whom serum measles antibody titers were assayed, 8 had antibody levels of less than 1:10. The commonest associated disease tabulated by Kipps et al. [49] was ALL; other diseases were chronic diarrhea, ganglioneuroma, neuroblastoma, lymphosarcoma, rhabdomyosarcoma and renal trans-



**Fig. 3.** Retina. Curved tubules characteristic of paramyxovirus. Formalin-fixed. Postfixed in glutaraldehyde.  $\times 152,000$ . (Kindness of Eva Chan, C.L. Dolman, and J. Rootman.)

plantation. Graham et al. [50] described a case in an adult with hypogammaglobulinemia.

For many years the variable clinical picture of SSPE has been well known. Risk and Haddad [35] emphasized the varying natural history of the disease. Kipps et al. [49] tried to separate four CNS syndromes associated with measles: acute measles due to direct invasion of the CNS by virus or an allergic encephalomyelitis, delayed acute encephalitis with immunosuppression, delayed acute encephalitis without immunosuppression, and

delayed subacute encephalitis (SSPE). In view of the protean clinical manifestations of SSPE it is hard to make a distinction between the delayed acute encephalitis without immunosuppression and SSPE clinically. Pathologically both are characterized by the presence of Cowdry's type A inclusions at the light-microscopic level, and paramyxovirus particles electron-microscopically. Probably the degree of damage to gray and white matter, particularly the degree of demyelination, and the amount of inflammation reflect how long the disease has been present and do not afford a morphological basis to separate delayed acute encephalitis without immunosuppression from SSPE.

A great advance in our understanding of SSPE came with the work of Choppin et al. [51]. They reported the absence of antibody to the M protein of the virus. The M protein is an internal membrane protein which plays a key role in the assembly of the virus particle by budding from the plasma membrane. It interacts with glycoproteins inserted in the cell membrane and the viral nucleocapsid.

One of the long-standing disputes about SSPE is whether it is due to a defective or mutant virus, or to a defect in the host's immunity. Hall and Choppin [32] interpreted their data to indicate that SSPE was due to a host-cell-dependent lack of synthesis of M protein, and was not due to a defective virus. In 1986, Cattaneo et al. [52] described a strain of SSPE virus in which 'the normal, monocistronic M mRNA was completely substituted by a bicistronic RNA containing the coding sequence of the preceding phosphoprotein (P) gene in addition to the M-coding sequence. Analysis of the intercistronic P-M region by direct cDNA sequencing showed that the consensus sequence at this RNA processing site was unaltered but revealed several different point mutations. cDNA cloning and sequencing of the entire M-coding region established that one of the point mutations leads to a stop codon at triplet 12 of the M-reading frame.' These workers go on to state that it is still not settled whether the genetic defects are stable genetic alterations of replicating viral genomes or whether the genetic defects are imposed by the immune response restricting viral functions by unknown mechanisms.

Roos et al. [53] described a patient with MIBE in an immunosuppressed host whose serum produced trace precipitation to P and L proteins of the measles virus and no precipitation of M protein on electrophoresis. They interpreted their data to indicate the 'MIBE is an opportunistic defective measles virus in the immunosuppressed.'

In neither of our cases were we able to culture measles virus by ordinary methods; true also of the case reported by Roos et al. [53]. Culture of the measles virus from patients with SSPE requires cocultivation, which may prove to be true of MIBE. The lack of M protein in one case of MIBE, and the inability to culture measles by ordinary means in those instances where the measles virus infection occurs in an immunosuppressed host may be further suggestive evidence that a defective measles virus is involved.

The diagnosis of MIBE in life may be difficult, particularly in those cases where measles antibodies are low. The presence of *epilepsia partialis continua* in the setting of an immunodeficient individual, particularly a child, with the characteristic EEG findings of unilateral or bilateral high-amplitude slow waves and periodic lateralizing epileptiform discharges should lead to a high level of suspicion of the diagnosis [54]. Brain biopsy is a possibility, but in both our cases the involvement of cortex was so focal and patchy, it would have been easy to take a biopsy from a perfectly normal-appearing area and thus fail to make the diagnosis.

At present, there is no known treatment for SSPE or MIBE. Simpson and Eden [55] reported the case of a 4-year-old boy with ALL in remission, who developed an encephalopathy following an attenuated measles vaccine. The boy's deterioration was halted when he was treated with interferon. Our patient did not respond to interferon, which was similar to the two cases treated with interferon by Olding-Stenkvis et al. [56]. Pathological diagnosis: MIBE in an immunocompromised host.

### Acknowledgement

We thank Dr. S. Pritchard, whose patient this was, for giving us permission to publish this case, and for reviewing the clinical history.

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